Subcutaneous anti-COVID-19 hyperimmune immunoglobulin for prevention of disease in asymptomatic individuals with SARS-CoV-2 infection: a double-blind, placebo-controlled, randomised clinical trial

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Summary

Background **Anti-COVID-19 hyperimmune immunoglobulin (hIG) can provide standardized and controlled antibody content. Data from controlled clinical trials using hIG for the prevention or treatment of COVID-19 outpatients have not been reported. We assessed the safety and efficacy of subcutaneous anti-COVID-19 hyperimmune immunoglobulin 20% (C19-IG20%) compared to placebo in preventing development of symptomatic COVID-19 in asymptomatic individuals with SARS-CoV-2 infection.**

eClinicalMedicine 2023;57: 101898

Published Online xxx https://doi.org/10.1016/j.eclinm.2023.101898

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Methods We did a multicentre, randomized, double-blind, placebo-controlled trial, in asymptomatic unvaccinated adults (≥18 years of age) with confirmed SARS-CoV-2 infection within 5 days between April 28 and December 27, 2021. Participants were randomly assigned (1:1:1) to receive a blinded subcutaneous infusion of 10 mL with 1 g or 2 g of C19-IG20%, or an equivalent volume of saline as placebo. The primary endpoint was the proportion of participants who remained asymptomatic through day 14 after infusion. Secondary endpoints included the proportion of individuals who required oxygen supplementation, any medically attended visit, hospitalisation, or ICU, and viral load reduction and viral clearance in nasopharyngeal swabs. Safety was assessed as the proportion of patients with adverse events. The trial was terminated early due to a lack of potential benefit in the target population in a planned interim analysis conducted in December 2021. ClinicalTrials.gov registry: NCT04847141.

Findings 461 individuals (mean age 39.6 years [SD 12.8]) were randomized and received the intervention within a mean of 3.1 (SD 1.27) days from a positive SARS-CoV-2 test. In the prespecified modified intention-to-treat analysis that included only participants who received a subcutaneous infusion, the primary outcome occurred in 59.9% (91/152) of participants receiving 1 g C19-IG20%, 64.7% (99/153) receiving 2 g, and 63.5% (99/156) receiving placebo (difference in proportions 1 g C19-IG20% vs. placebo, –3.6%; 95% CI -14.6% to 7.3%, $p = 0.53$; 2 g C19-IG20% vs placebo, 1.1%; –9.6% to 11.9%, $p = 0.85$). None of the secondary clinical efficacy endpoints or virological endpoints were significantly different between study groups. Adverse event rate was similar between groups, and no severe or life-threatening adverse events related to investigational product infusion were reported.

Interpretation Our findings suggested that administration of subcutaneous human hyperimmune immunoglobulin C19-IG20% to asymptomatic individuals with SARS-CoV-2 infection was safe but did not prevent development of symptomatic COVID-19.

Funding Grifols.

Keywords: Hyperimmune immunoglobulin; Antibody therapies; COVID-19; SARS-CoV-2; Outpatients; Asymptomatic individuals

Research in context

Evidence before this study

We searched the PubMed database for articles (including preprints) published between April 2020 and October 2022, and reporting results from randomised trials evaluating the effect of hyperimmune immunoglobulins (hIG) for the prophylaxis or treatment of SARS-CoV-2 infected individuals. We used various combinations of the terms "COVID-19", "COVID", "SARS-CoV-2", "Coronavirus", "hyperimmune immunoglobulin", "intravenous immunoglobulin", "hIG", or "hIVIG", "passive immunotherapy", "passive immunization", "plasma therapy", and "clinical trial". The search retrieved only three trials (two pilot studies and an international multicentre study funded by the NIH) evaluating the safety and efficacy of hIG therapies for COVID-19, all of which included only hospitalised patients with COVID-19 and administered intravenous infusion of hIG. No trials were found evaluating the safety and efficacy of hIG therapies in outpatients with SARS-CoV-2 infection.

Added value of this study

This study is the first placebo-controlled randomised clinical trial to report results of anti-COVID-19 hIG as pre-emptive therapy for asymptomatic individuals with confirmed SARS-CoV-2 infection. We found that, compared to placebo, subcutaneous human hyperimmune immunoglobulin C19-IG20% at the dose of either 1 g or 2 g did not reduce the risk of developing symptomatic COVID-19 when administered to asymptomatic individuals with confirmed SARS-CoV-2 infection within 5 days, regardless of risk factors. There was no heterogeneity of treatment effect in efficacy among individuals without endogenous antibodies, nor in any of the other subgroup analyses conducted. There were no significant differences in the safety endpoints, including the proportion of treatment-emergent adverse events and severe adverse events between groups.

Implications of all the available evidence

Our results do not support the use of subcutaneous C19-IG20% in asymptomatic individuals with SARS-CoV-2 infection to prevent symptomatic COVID-19. Our findings indicate that C19-IG20% is safe and well tolerated if administered at the dose of either 1 g or 2 g.

Introduction

Anti-SARS-CoV-2 antibody products have emerged as promising candidates for the treatment and prophylaxis of COVID-19 since the beginning of the pandemic. Five anti-SARS-CoV-2 monoclonal antibody (mAb) products have shown clinical benefit when used to treat COVID-19 outpatients[1–6] and hospitalised patients without detectable antibodies to SARS-CoV-2,[7–9] as well as for pre- and post-exposure prophylaxis.[10–12] However, the efficacy of these mAb therapies can be affected by antigenic shifts of new circulating variants. Currently, all mAbs for the treatment of COVID-19 have shown to be ineffective *in vitro* against the Omicron variant and its subvariants.[13–23] COVID-19 Convalescent Plasma (CCP), an alternative antibody product that contains polyclonal antibodies from donors who have recovered from infection, has proven not to reduce mortality in hospitalised patients.[24–27] CCP has been also tested in outpatients with COVID-19 with mixed results. Positive results were driven by very early administration of CCP (≤5 days after symptoms onset) and high antibody titers.[28–33]

A high-titre and high-concentration antibody preparation can be produced by pooling plasma collected from multiple donors who have recovered from COVID-19, resulting in the so-called anti-COVID-19 hyperimmune immunoglobulin (hIG). The use of hIG preparations has been established for the treatment and prophylaxis of several viral infections, including cytomegalovirus, varicella, rubella, and hepatitis B and A.[34–36] However, clinical data on the use of hIG for COVID-19 are limited to three clinical trials administering the product intravenously to hospitalised patients. The first one, a small single-centre trial of 50 COVID-19 severely or critically ill patients, reported nonsignificant reductions in mortality associated with hIVIG compared to the standard of care.[37] The second trial (ITAC) was an international multicentre study funded by the US National Institute of Health (NIH) that randomized 593 hospitalised COVID-19 patients without end-organ failure to receive either hIVIG or an equivalent volume of saline as placebo in addition to standard clinical care. The trial showed no significant improvement of the clinical status, measured by a seven-category ordinal scale.[38] The third trial showed a reduction in the risk for severe COVID-19 in 18 severely immunocompromised hospitalised patients.[39]

C19-IG20% is a subcutaneous formulation containing 20% human hIG that consists of purified protein from pooled plasma donations, with IgG accounting for at least 98% of the protein. C19-IG20% has some advantages over other anti-SARS-CoV-2 antibody products. First, unlike mAbs, the polyclonal nature of its antibodies could mitigate the immune evasion of emerging viral variants. Second, it contains a standardized and controlled high-titre content of neutralizing antibodies, overcoming the inter-unit variability of CCP. It is also subjected to robust pathogen reduction rendering it virally safe, and it is purified by technologies demonstrated to preserve immunoglobulin neutralization capacity and Fc fragment integrity. Third, unlike most mAbs and other hIG evaluated so far, which need to be administered intravenously, C19-IG20% is available for subcutaneous infusion, allowing easier and faster administration at the primary care level in the outpatient setting. To date, data from controlled clinical trials using hIG products for prophylaxis or treatment of COVID-19 outpatients have not been reported. We evaluated the safety and clinical efficacy of the subcutaneous C19-IG20% in reducing the risk of developing symptomatic COVID-19 in asymptomatic individuals with SARS-CoV-2 confirmed infection.

Methods

Trial design

The GC2010 trial was a multicentre, double-blinded, randomised (1:1:1), parallel group study to assess the safety and efficacy of the anti-COVID-19 hyperimmune immunoglobulin (Human) 20% (C19-IG20%) in preventing symptomatic COVID-19 in asymptomatic outpatients with SARS-CoV-2 infection. The trial was conducted between April 28, 2021, and December 27, 2021, at seven healthcare administrative regions providing universal healthcare to a catchment population of around 12 M people in Spain (Methods S1, Supplementary Appendix).

The study was conducted according to the Helsinki Declaration of the World Medical Association, and the study protocol was approved by the Ethics Committee at Hospital Germans Trias i Pujol (number PI 21-015) and the institutional review boards of the rest of participating centres. All patients provided informed consent before enrolling in the study, which was supervised by an independent data and safety monitoring board. This trial was registered in ClinicalTrials.gov (NCT04847141). The protocol and statistical analysis plan are available in the supplementary materials.

Participants and recruitment

We included asymptomatic individuals aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection within 5 days prior to randomization. SARS-CoV-2 infection was determined by RT-PCR, rapid antigen test, or transcription-mediated amplification (TMA) test. Candidates were considered to be asymptomatic if they had no fever (oral temperature ≥38 °C), cough, shortness of breath, fatigue, anorexia, vomiting/diarrhoea, myalgias, headache, olfactory disorders, or pneumonia at screening. Individuals were excluded from the study if they required hospitalisation for any cause or had an oxygen saturation level (SpO2) of ≤94% on room air, or a National Early Warning Score (NEWS) > 2 points at the baseline visit. Additionally, individuals were

excluded if they had received a complete or incomplete regimen of COVID-19 vaccination, were taking agents with antiviral activity against SARS-CoV-2 and/or convalescent COVID-19 plasma or had contraindications to the investigational product. Female participants who were pregnant, breastfeeding or planning a pregnancy during the study were also excluded. Further details on the eligibility criteria are listed in Methods S2.

Potential eligible participants were identified by searching the database systems for SARS-CoV-2 positive individuals nationwide. The investigators contacted candidates by phone in order to explain the study, invite them to participate, and obtain their oral consent to participate in the screening process. Within 24 h, investigators conducted a baseline visit (day 1) at the home of suitable candidates, during which written informed consent was obtained and eligibility was confirmed.

Randomisation and masking

Participants were randomly assigned using a central web-based randomization system to receive either a 1 g dose of C19-IG20%, a 2 g dose of C19-IG20%, or sterile 0.9% saline solution (placebo). Randomization was stratified by age (<65 years vs. ≥65 years). An unmasked nurse, who was completely independent of the evaluating study team, conducted the randomization after the investigators had confirmed eligibility. The unmasked nurse prepared and administered the blinded investigational product. All participants and investigators were masked to the treatment allocations, including follow-up personnel, laboratory personnel, and statisticians, with the exception of unmasked nurses. The randomization and administration of the investigational product were always conducted on the first day of the study (baseline visit, day 1).

Investigational products and procedures

Both, the investigational product and placebo, were administered with a 10 mL subcutaneous infusion over 10–20 min (1–2 min per mL) on day 1. The investigational product (i.e., C19-IG20%) (prepared and provided by Grifols) was a sterile liquid formulation of immunoglobulin purified from human plasma with high-anti-SARS-CoV-2 antibodies collected from donors recovered from COVID-19 from May 2020 to July 2020. The criteria for the selection of convalescent plasma units were anti-SARS-CoV-2 antibody titre corresponding to ≥10.0 using the Ortho-Vitros method or ≥7.0 using the Architect-Abbott method. The highest dose of 2 g was selected based on the volume that can be safely administered subcutaneously without the need of a peristaltic pump and the maximum lyophilizing capacity of the manufacturer. Further details on the preparation, manufacturing, and characteristics of the C19-IG20% are provided in Methods S3. The neutralizing activity of C19-IG20% was assessed against the virus lineage Wuhan-Hu-1, the alpha (B.1.1.7), beta (B.1.351) and delta (B.1.617.2) VOC (Methods S4), using a pseudovirus neutralization assay, as part of a post-hoc analysis. The distribution of VOC during plasma collection and recruitment periods are shown in Methods S5. Participants were all provided with pulse oximeters and thermometers for daily self-recording of their SpO2 and body temperature at home. In-person follow-up visits were planned for study days 3, 7, 14, and 29 at the participants' residences, or in the hospital if they were hospitalised. Additionally, investigators contacted study participants by telephone on study days 5, 9, and 11 to assess their clinical status, including the development of symptomatic COVID-19, and to record their daily SpO2 and body temperature measurements. We performed a final telephone check on day 60 to assess vital status, hospital admissions, ICU admissions, requirement for invasive mechanical ventilation and adverse events. All collected data were recorded in an electronic case report form.

Nasopharyngeal swabs were obtained for quantification of SARS-CoV-2 viral load on study days 1, 3, 7, 14, and 29. Blood samples were obtained on days 1, 7, and 14 to assess inflammatory biomarkers (D-dimer, ferritin, and C-reactive protein [CRP]), biochemical and haematology parameters (creatinine, albumin, ALT, total bilirubin, LDH, haemoglobin, haematocrit, platelet count, absolute neutrophil and lymphocyte counts, and leukocyte counts) and levels of anti-SARS-CoV-2 antibodies (IgM and IgG).

Viral load was analysed by real-time quantitative RT-PCR in two consecutive steps, viral RNA extraction using QIAmp MinElute Virus Spin kit (Qiagen) and amplification/detection by TaqPath COVID-19 CE-IVD RT-PCR kit (Thermo Fishe Scientific) at a centralized laboratory (Progenika Clinical Diagnostics Laboratory, Progenika Biopharma, a Grifols company, Derio, Spain). For absolute quantification, a standard curve was built using serial dilutions of a SARS-CoV-2 plasmid RNA of known concentration (EVAg), run in parallel to a set of samples covering all thermal cycles used in the analysis (Methods S6). SARS-CoV-2 IgM and IgG antibodies were tested using AESKULISA® SARS-CoV-2 S1 IgG and IgM test (AESKU Enzyme Linked Immunosorbent Assay), processed on the SQII Elisa Analyzer (AESKU), at Progenika Clinical Diagnostics Laboratory under specifications described by provider (Methods S7).

Outcomes

The primary outcome was the proportion of participants who remained asymptomatic through day 14. Symptomatic COVID-19 was defined as fulfilling one of the following four conditions: (1) developing at least two of the following predefined systemic symptoms: fever ≥38 °C, chills, myalgia, headache, sore throat, cough, fatigue that interfered with daily activities, new olfactory or taste disorders, vomiting or diarrhoea; or (2)

experiencing at least one of the following respiratory signs/symptoms: new or worsening shortness of breath or difficulty breathing; or (3) experiencing SpO2 <94% on room air; or (4) having radiographical evidence of pneumonia.

Prespecified secondary clinical outcomes included the proportion of individuals who presented one of the following non-mutually exclusive events: participants who remained in an outpatient setting and maintained SpO2 ≥94% through day 14, and participants who required oxygen supplementation, required any medically attended visit for management or treatment of COVID-19, hospitalisation, or ICU admission through day 29. Time to the onset of COVID-19 symptoms was also analysed.

Secondary virological outcomes included viral load reduction in nasopharyngeal swabs on days 7 and 14 and viral clearance by RT-PCR on days 14 and 29. Other secondary outcomes included change in inflammatory parameters (D-dimer, ferritin, and C-reactive protein [CRP]) from baseline to day 14 of follow-up and change in quantitative anti-SARS-CoV-2 antibodies through day 14.

Safety was assessed by the proportion of patients experiencing treatment-emergent adverse events (TEAEs), defined as the adverse events (AEs) that occurred on or after the time of investigational product administration; and the clinically significant change in key biochemical parameters of organ function/dysfunction (creatinine, albumin, alanine aminotransferase (ALT), total bilirubin, LDH, haemoglobin, haematocrit, platelet count, absolute neutrophil and lymphocyte counts, and leukocyte counts) from baseline to day 14.

Statistical analysis

We estimated that a sample size of 801 (267 cases per arm) would provide the trial with 80% power to detect an increase of 10% in the proportion of asymptomatic participants remaining asymptomatic after treatment, assuming an expected proportion remaining asymptomatic of 80%, at a significance level of $\alpha = 0.025$, and allowing a 10% withdrawal rate.

Primary efficacy analyses were performed on the modified intention-to-treat (m-ITT) population, which included all the randomized participants who received any interventional product infusion. Sensitivity analyses were performed with the intention-to-treat (ITT) population (i.e., all randomized participants) and the per-protocol (PP) population (i.e., participants completing the follow-up without major protocol deviations which might have an impact on the primary efficacy endpoints, and complete at least 80% of the interventional product). Safety was assessed in the safety population, which included all randomized participants who received at least any amount of blinded interventional product infusion.

The baseline characteristics of the study population were summarized descriptively using the number of non-missing observations, mean, standard deviation (SD), median and interquartile range (IQR) for the continuous/quantitative data or absolute and relative frequency counts and percentages for categorical/qualitative data. The primary clinical efficacy endpoint was compared between the two doses of C19-IG20% and placebo using the Cochran-Mantel-Haenszel (CMH) test adjusting for age. Subgroup analyses of the primary clinical efficacy endpoint and analyses of secondary clinical efficacy endpoints were assessed using the Fisher's exact test or Chi-square test.

The secondary efficacy endpoint of change in SARS-CoV-2 viral load ($\log_{10}$ copies/mL) from baseline to day 7 and day 14 was assessed by an analysis of covariance (ANCOVA) with treatment and randomization strata as fixed effects and baseline value as covariate. Time-to-event outcomes were assessed using Kaplan–Meier estimates. Between-arm analysis for other secondary outcomes were done using parametric or non-parametric methods according to its distributions. Non-parametric methods were used for non-normal distributed variables with right-skewed distributions (IgG/IgM variables and laboratory markers) and the assessment of distribution was verified visually. One-way ANOVA or Kruskal–Wallis test for the comparison between all three treatment arms and Student's t or Dunn's tests for the pairwise comparison using Holm's method for p-value correction. All statistical tests were performed in the SAS statistical software under a significance level of 0.05.

Role of the funding source

This study was funded by Grifols. Five authors were employees from Grifols and made substantial contributions to study design (EM), data analysis (YT), and manuscript revision (EM, MT, NC, AS, YT). Other authors, independent from the study funder, were also involved in all of the aforementioned tasks, as described in the authors' contributions disclosure. MT had full access to the data set, as did OM, AA, and DO.

Results

Study setting and patient characteristics

Between 28 April 2021 and 27 December 2021, our team identified and contacted approximately 3000 individuals with confirmed SARS-CoV-2 infection, many of whom presented with COVID-19 symptoms and were therefore not eligible. We screened 555 asymptomatic individuals with confirmed SARS-CoV-2 infection. Fig. 1 summarizes the recruitment and follow-up of study participants. Among 555 individuals screened, 461 met all the selection criteria and received the allocated intervention, thereby being included in the m-ITT analysis: 152 received 1 g C19-IG20%, 153 received 2 g

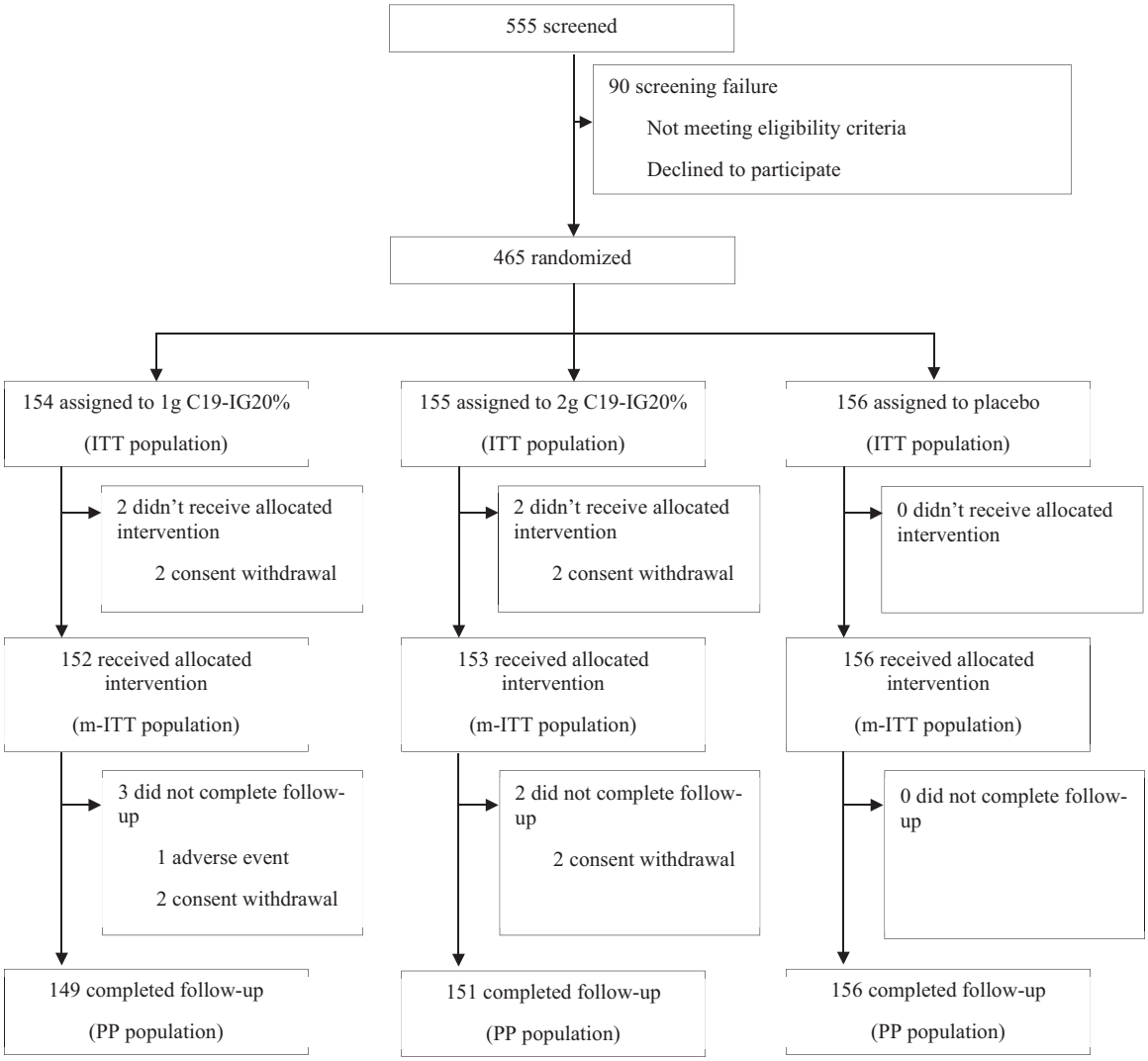

***Fig. 1:* Trial profile**. ITT, intention to treat; m-ITT, modified intention to treat; PP, per protocol.

C19-IG20% and 156 received placebo (Table S1, Supplementary Appendix). All participants included in the m-ITT analysis completed their infusion.

Neutralizing activity of C19-IG20% was evaluated using pseudoviral neutralization assay against the original Wuhan SARS-CoV-2 strain and alpha (B.1.1.7), beta (B.1.351), and delta (B.1.617.2) variants. A 2.4 and 2.9-fold decrease in neutralizing antibody titres was observed against alpha and delta variants, respectively, compared with Wuhan-Hu-1 (geometric mean ID50 13510 for alpha and 11367 for delta vs ID50 32917 for Wuhan-Hu-1) (Methods S4).

The baseline demographic and clinical characteristics were similar in the three groups (Table 1). Overall, study participants had a mean age of 39.6 (SD 12.8) years, 197 (42.7%) of 461 participants were women, and 101 (21.9%) had at least one comorbidity. The mean time from positive SARS-CoV-2 test to random allocation was 3.1 (SD 1.3) days, and the mean time from exposure to random allocation (among 160 of 461 participants in which the potential contact with SARS-CoV-2 could be identified) was 5.6 (SD 2.8) days.

Participants were allocated to a treatment arm and infused (blinded administration) on the same day. Baseline serum antibody results for IgM/IgG were negative for 345 (80%) of the 431 participants for whom results were available. Prior to recruitment, all individuals had a documented positive SARS-CoV-2 test result (either by antigen detection or by DNA detection tests), according to inclusion criteria. However, at baseline, 119 (26%) of 461 participants had a negative SARS-CoV-2 RT-PCR result and 342 (74%) participants had a positive RT-PCR test result. In total, 372 (81%) of the participants had a positive RT-PCR result at any time

	1 g C19-IG20% N = 152	2 g C19-IG20% N = 153	Placebo N = 156
Demographics			
Age, years – mean (SD)	38.8 (12.8)	41.1 (12.4)	38.8 (13.3)
Age group – n (%)			
18–65 years	146 (96.1)	147 (96.1)	149 (95.5)
≥65 years	6 (3.9)	6 (3.9)	7 (4.5)
Women – n (%)	66 (43.4)	62 (40.5)	69 (44.2)
Men – n (%)	86 (56.6)	91 (59.5)	87 (55.8)
BMI (kg/m2) – mean (SD)	26.0 (4.7)	26.4 (5.1)	25.5 (4.4)
SARS-CoV-2 infection characteristics			
Days from positive test[a] to random assignment[b], days – mean (SD, N)	3.1 (1.2, 152)	3.1 (1.4, 153)	3.0 (1.2, 156)
Days from exposure[c] to random assignment[b], days – mean (SD, N)	5.8 (2.8, 56)	5.2 (2.5, 58)	5.7 (3.3, 46)
Comorbidities – n (%)			
At least one comorbidity	35 (23.0)	39 (25.5)	27 (17.3)
Obesity (BMI ≥30 kg/m2)	29 (19.1)	30 (19.6)	18 (11.5)
Diabetes Mellitus	5 (3.3)	11 (7.2)	7 (4.5)
Hypertension	11 (7.2)	11 (7.2)	10 (6.4)
Heart conditions (i.e. heart failure, coronary artery disease, cardiomyopathies)	2 (1.3)	1 (0.7)	1 (0.6)
Chronic Obstructive Pulmonary Disease	0 (0.0)	1 (0.7)	1 (0.6)
Asthma	10 (6.6)	7 (4.6)	9 (5.8)
Chronic kidney disease	1 (0.7)	2 (1.3)	1 (0.6)
History of cancer	3 (2.0)	1 (0.7)	3 (1.9)
Immunocompromised state from solid organ transplant	0 (0.0)	0 (0.0)	0 (0.0)
Serum IgM and IgG antibody status – n (%)			
N[d]	139	146	146
Negative	114 (82)	118 (81)	113 (77)
Positive	25 (18)	28 (19)	33 (23)
Study RT-PCR – n (%)			
Positive at baseline	110 (72)	108 (71)	124 (79)
Negative at baseline	42 (28)	45 (29)	32 (21)
Positive at any time during the study	120 (79)	118 (77)	134 (86)
Positive at baseline and IgM and IgG negative at baseline	77 (51)	80 (52)	83 (53)
Viral load			
Mean Viral Load (SD) in log_{10}	5.8 (2.6)	5.8 (2.6)	6.1 (2.4)
Laboratory parameters – mean (SD)			
N[e]	148	152	153
D-dimer (mg/L)	0.6 (1.5)	0.4 (0.4)	0.6 (2.6)
Ferritin (ug/L)	111.2 (120.2)	115.2 (138.2)	123.7 (163.4)
C-reactive protein (CRP) (mg/dl)	5.8 (10.5)	6.4 (6.7)	5.9 (6.4)

BMI = body mass index; SD = standard deviation. Laboratory reference ranges: D-dimer 0-0.50 mg/L; Ferritin 30.0–400.0 ug/L; C-reactive protein 0.0–1.0 mg/dL. [a]First positive PCR (RT-PCR), NAT or other commercial or public health assay result for SARS-CoV-2 infection. [b]Random assignment and infusion were always done on the same day. [c]Exposure in terms of first potential contact with virus. [d]30/461 participants did not have baseline serological test (13/152 in the 1 g C19-IG20% group; 7/153 in the 2 g C19-IG20% group; and 10/156 in the placebo group). Missing data in this variable can be assumed random. [e]8/461 participants did not have baseline laboratory parameters (4/152 in the 1 g C19-IG20% group; 1/153 in the 2 g C19-IG20% group; and 3/156 in the placebo group). Missing data in this variable can be assumed random.

Table 1: **Baseline characteristics in the modified intention-to-treat population.**

during the study. The mean viral load from the nasopharyngeal swab at baseline was 5.8 (SD 2.6) log_{10} copies per mL in the 1 g C19-IG20% group, 5.8 (SD 2.6) log_{10} copies per mL in the 2 g C19-IG20% group and 6.1 (SD 2.4) log_{10} copies per mL in the placebo group.

Trial enrolment was halted on December 27, 2021, based on the results of a planned interim analysis of all available data on primary and secondary efficacy outcomes, which concluded the lack of potential benefit of the intervention in the target population. This article presents the final and only report analysis after early termination.

Clinical efficacy outcomes

In the modified ITT population, the primary outcome analyses (i.e., the proportion of participants who remained asymptomatic on day 14) did not differ significantly between placebo-treated and C19-IG20%-treated individuals, irrespective of the dose received (Table 2). The primary outcome occurred in 59.9%

	1 g C19-IG20% N = 152	2 g C19-IG20% N = 153	Placebo N = 156	Difference in proportions 1 g C19-IG20% - Placebo (95% CI)	p-value	Difference in proportions 2 g C19-IG20% - Placebo (95% CI)	p-value
Primary clinical efficacy endpoint through day 14							
Remained asymptomatic – n(%)	91 (59.9)	99 (64.7)	99 (63.5)	−3.6 (−14.6 to 7.3)	0.526	1.1 (−9.6 to 11.9)	0.846
Developed ≥2 systemic COVID-19 symptoms[a]	58 (38.2)	54 (35.3)	54 (34.6)	3.6 (−7.3 to 14.5)	0.527	0.8 (−9.9 to 11.5)	0.894
Experienced ≥1 respiratory symptoms[b] (new or worsening shortness of breath, difficulty breathing)	9 (5.9)	8 (5.2)	15 (9.6)	−3.6 (−9.7 to 2.4)	0.245	−4.4 (−10.2 to 1.4)	0.14
Experienced Sp02 < 94% on room air	5 (3.3)	3 (2.0)	3 (1.9)	1.4 (−2.1 to 5.0)	0.439	0.0 (−3.1 to 3.1)	0.988
Had radiographical evidence of pneumonia	6 (3.9)	7 (4.6)	3 (1.9)	2.1 (−1.7 to 5.9)	0.274	2.8 (−1.2 to 6.8)	0.175
Subgroup analyses of the primary clinical efficacy endpoint: remained asymptomatic through day 14							
Positive PCR results at study baseline	59/110 (53.6)	61/108 (56.5)	74/124 (59.7)	−6.1 (−18.7 to 6.9)	0.352	−3.2 (−15.9 to 9.8)	0.623
Positive PCR results at any time during the study	65/120 (54.2)	68/118 (57.6)	84/134 (62.7)	−8.5 (−20.8 to 3.7)	0.169	−5.1 (−17.3 to 7.1)	0.413
Positive IgM/IgG results at baseline	20/25 (80.0)	26/28 (92.9)	28/33 (84.8)	−4.8% (−15% to 24.7%)	0.628	8% (−23.5% to 7.5%)	0.328
Negative IgM/IgG results at baseline	65/114 (57.0)	68/118 (57.6)	66/113 (58.4)	−1.4% (−12.3% to 15.1%)	0.938	0.8% (−12.7% to 14.3%)	1.000
Secondary clinical efficacy endpoints							
Remained in an outpatient setting and maintained Sp02 ≥ 94% through day 14	141/148 (95.3)	140/149 (94.0)	148/154 (96.1)	−0.8 (−6.1 to 4.2)	0.721	−2.1 (−7.8 to 3.1)	0.390
Required oxygen supplementation through day 29	3/152 (2.0)	6/153 (3.9)	2/156 (1.3)	0.7 (−2.9 to 4.6)	0.631	2.6 (−1.2 to 7.3)	0.144
Required ≥1 related medically attended visit through day 29	26/152 (17.1)	29/153 (19.0)	22/156 (14.1)	3 (−5.3 to 11.5)	0.468	4.9 (−3.6 to 13.4)	0.251
Required hospitalisation through day 29	3/152 (2.0)	7/153 (4.6)	3/156 (1.9)	0.1 (−3.8 to 4.0)	0.974	2.7 (−1.6 to 7.5)	0.188
Required ICU admission through day 29	1/152 (0.66)	1/153 (0.65)	1/156 (0.64)	0.02 (−3.05 to 3.12)	0.985	0.01 (−2.99 to 3.07)	0.989

Risk difference for the proportions of subjects between groups using CMH (Cochran-Mantel-Haenszel) method adjusted by age for primary efficacy endpoints and Chi-square for secondary clinical efficacy endpoints. [a]Systemic symptoms: fever (≥38 °C), chills, myalgia, headache, sore throat, cough, fatigue that interfered with daily activities, new olfactory/taste disorder, vomiting/diarrhoea (note that new olfactory/taste disorder and vomiting/diarrhoea only counted as one item of definition). [b]New or worsening shortness of breath or difficulty breathing.

Table 2: **Clinical trial efficacy end points in the modified intention-to-treat population.**

(91/152) of participants receiving 1 g C19-IG20%, 64.7% (99/153) receiving 2 g, and 63.5% (99/156) receiving placebo (difference in proportions: 1 g C19-IG20% vs. placebo, –3.6%; 95% CI -14.6% to 7.3%, p = 0.53; 2 g C19-IG20% vs. placebo, 1.1%; –9.6% to 11.9%, p = 0.85). The most common presentation among symptomatic participants was a combination of two or more systemic COVID-19 symptoms. Only a small proportion of participants experienced ≥1 respiratory symptoms, SpO2 <94%, or had radiographic evidence of pneumonia. The analysis of the primary outcome in the ITT population (Table S2) and the PP population (Table S3) also revealed no significant differences between participants treated with placebo versus those treated with C19-IG20%. We conducted post-hoc analyses of the primary efficacy endpoint in sub-groups according to the study RT-PCR test result (baseline and throughout the follow-up) and serological status of participants at baseline. None of the sub analyses revealed significant differences between groups regarding the primary endpoint (Table 2). Sensitivity analysis of primary efficacy endpoints stratified by age and comorbidities were also performed, finding no differences between groups (Table S4).

Regarding secondary clinical efficacy outcomes, overall, 11 (2.4%) participants required oxygen supplementation at some point during the follow-up, 77 (16.7%) required one or more COVID-19 related medical visits, 13 (2.8%) required hospitalisation and 3 (7.2%) required admission to an ICU. No participants in any treatment group required invasive mechanical ventilation and no participants died during the study. None of these secondary endpoints were significantly different between study groups (Table 2). Time to the onset of COVID-19 symptoms did not show significant differences between groups; 30% of study participants developed symptoms within the first three days after infusion (Fig. S1).

Other efficacy outcomes

Fig. 2 shows the SARS-CoV-2 viral load decay throughout the follow-up period. We found no significant differences between groups regarding the mean difference in viral load from baseline to day 7 (absolute difference 0.10 $\log_{10}$ copies/mL for C19-IG20% 1 g vs. placebo [95% CI -0.24 to 0.44; p = 0.58]; and –0.17 for C19-IG29% 2 g vs. placebo [95% CI -0.52 to 0.17; p = 0.33]) and from baseline to day 14 (0.11 for

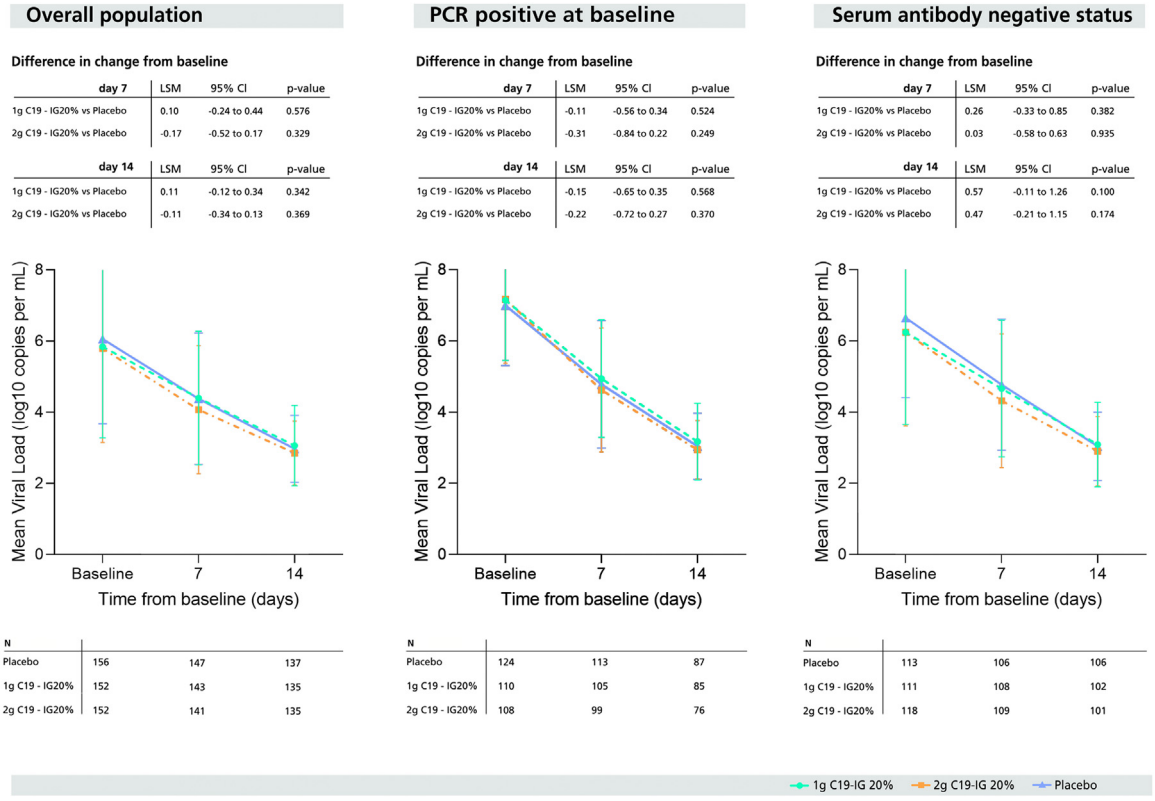

***Fig. 2*: Viral load change over 14 days**. Figure shows the mean viral load (in $\log_{10}$ copies per millilitre) at baseline, day 7 and day 14 in the overall population and in subgroup of PCR positive at baseline and serum antibody negative status (IgM/IgG negative at baseline). Tables on the figure show difference in least-squares means (LSM) of change from baseline to day 7 and day 14 of viral load (in $\log_{10}$ copies per millilitre) for both doses of C19-IG20% compared to placebo in the overall population and in subgroup of PCR positive at baseline and serum antibody negative status. 95% CI for difference in LSM between each of C19-IG20% dose groups (1 g and 2 g) and placebo and the associated p-value were calculated using an ANCOVA model, including the change from baseline value as a dependent variable; treatment group as a fixed effect; and baseline viral load value, age, and gender as covariates.

C19-IGG20% 1 g vs. placebo [95% CI -0.12 to 0.34; $p = 0.34$] and –0.11 for C19-IG29% 2 g vs. placebo [95% CI -0.34 to 0.13; $p = 0.37$]). Likewise, no differences were observed in time to viral clearance, assessed by RT-PCR up to day 29 (Figs. S2 and S3).

Changes in inflammatory parameters, including D-dimer, ferritin, and C-reactive protein (CRP), did not show significant differences between groups from baseline to day 14 of follow-up (Fig. S4). Likewise, the groups did not differ regarding the change in anti-SARS-CoV-2 IgM and IgG throughout the follow-up (Fig. S5).

Safety

Table 3 summarizes the TEAEs that occurred from the time of administration of the investigational product to day 14 of follow-up. A total of 359 TEAEs were reported: 137 TEAEs in 78/152 (51.3%) participants in the C19-IG20% 1 g group, 96 TEAEs in 65/153 (42.5%) in the C19-IG20% 2 g group, and 126 TEAEs in 72/156 (46.2%) in the placebo group, with no differences between treatment groups. Blinded investigators evaluated the 359 TEAEs and determined that 263 (73%) were not related to the investigational product and 10 (2.8%) were definitely related. Regarding the severity of the events, 286 (79.7%) were mild (Grade 1), 61 (17.0%) moderate (Grade 2), 10 (2.8%) severe (Grade 3), and 2 (0.5%) life-threatening (Grade 4). All TEAEs related to the investigational product were mild or moderate in severity. All severe and life-threatening TEAEs were related to COVID-19. No individuals experienced a TEAE leading to death. There were no serious adverse drug reactions reported.

Most common TEAEs were related to COVID-19, including gastrointestinal disorders, arthralgia, headache, cough, and fever. TEAEs related to IP infusion included injection site pain, puncture site pain and erythema, and vasovagal syndrome (Table S5). No severe allergic reactions or anaphylaxis and thromboembolic events were reported.

	1 g C19-IG20% (n = 152)		2 g C19-IG20% (n = 153)		Placebo (n = 156)		Difference in proportions 1 g C19-IG20% - Placebo (95% CI)	p-value	Difference in proportions 2 g C19-IG20% - Placebo (95% CI)	p-value
	Number of subjects[a]	Number of events[b]	Number of subjects[a]	Number of events[b]	Number of subjects[a]	Number of events[b]				
Treatment Emergent Adverse Events (TEAE)										
≥1 TEAE	78 (51.3)	137	65 (42.5)	96	72 (46.2)	126	−5.16% (−7.00% to 17.00%)	0.428	3.67% (−15.00% to 8.00%)	0.593
Relationship to investigational product										
Not related	48 (31.6)	97	43 (28.1)	69	53 (34.0)	97				
Possibly related	26 (17.1)	36	15 (9.8)	20	19 (12.2)	29				
Definitely related	4 (2.6)	4	6 (3.9)	6	0 (0.0)	0				
Severity										
Mild (Grade 1)	57 (37.5)	112	46 (30.1)	72	54 (34.6)	102				
Moderate (Grade2)	17 (11.2)	21	13 (8.5)	18	16 (10.3)	22				
Severe (Grade 3)	3 (2.0)	3	5 (3.3)	5	2 (1.3)	2				
Life threatening (Grade 4)	1 (0.7)	1	1 (0.7)	1	0 (0.0)	0				
Fatal (Grade 5)	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0				
TEAE leading to death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0				
TEAE leading to study withdrawal	1 (0.7)	1	0 (0.0)	0	1 (0.6)	1				
Treatment Emergent Serious Adverse Events (TE-SAE)										
≥1 TE-SAE	3 (2.0)	3	7 (4.6)	7	3 (1.9)	3	−0.05% (−3.00% to 3.00%)	1	−2.65% (−1.00% to 7.00%)	0.319
COVID-19 pneumonia	3 (2.0)		7 (4.6)		1 (0.6)					
Non-COVID-19 pneumonia	0 (0)		0 (0)		2 (1.3)					

AE = adverse event; IP = investigational product; SAE = serious adverse event; TEAE = treatment-emergent adverse event. Note: Treatment-emergent AEs are AEs that occurred on or after the date/time of IP administration. Percentages were based on the total number of safety subjects in each treatment group (N). [a]At each level of summation (overall, relationship, severity), subjects reporting more than one AE were counted only once using the strongest relationship to study drug and maximum severity. [b]Number of events included all occurrences of AEs.

Table 3: **Safety end points in the safety population.**

13 SAE were reported: 3 (2%) in the C19-IG20% 1 g group, 7 (4.6%) in the C19-IG20% 2 g group, and 3 (1.9%) in the placebo group. All SAEs were related to COVID-19 infection, except for two cases of pneumonia not related to COVID-19.

Change in biochemical and haematological parameters of organ derangement or systemic inflammatory response (i.e., creatinine, albumin, alanine aminotransferase (ALT), total bilirubin, LDH, haemoglobin, haematocrit, platelet count, absolute neutrophil and lymphocyte counts, and leukocyte counts) from baseline to day 14 did not show clinically relevant differences between groups (Table S6 and Fig. S6).

Discussion

Our findings show that early infusion with 1 g or 2 g of C19-IG20%, compared with placebo, did not reduce the risk of developing symptomatic COVID-19 in individuals diagnosed with asymptomatic SARS-COV-2 infection. Furthermore, neither our secondary clinical or virological endpoints nor our prespecified subgroup analyses demonstrated a benefit of this therapy. Safety endpoints, including the proportion of treatment-emergent adverse events (TEAEs) and severe adverse events (SAE) did not differ between the treatment groups and were mainly related to COVID-19. No severe or life-threatening events related to interventional product infusion were reported. Overall, these findings indicate that C19-IG20% at the dose of 1 g and 2 g is safe and well tolerated but did not prevent development of symptomatic COVID-19.

Passive immunotherapies, including hIG, mAbs and CCP, have demonstrated no clinical benefit in reducing the mortality risk in most hospitalised patients with COVID-19, except for selected groups (severely immunocompromised and seronegative).[7–9,24–27,37–39] As opposed to these studies, ours focused on outpatients with a very recent and asymptomatic infection since antibody products are expected to be more beneficial when administered very early in the course of infection. For example, early administration of mAbs and CCP has been demonstrated to have clinical benefits in outpatients with mild and moderate COVID-19.[1,3–6,30–32] Moreover, combinations of mAbs have been shown to reduce the risk of both asymptomatic and symptomatic SARS-CoV-2 infection when administered as pre- and post-exposure prophylaxis (PrEP and PEP).[10–12] Conversely, CCP (tested only as PEP) failed to prevent infection in asymptomatic contacts in a clinical trial conducted in the US.[40]

Our results did not reflect previous findings in the treatment of outpatients with mAbs and CCP, despite the very early administration of immune therapy. On the other hand, our results are consistent with the lack of benefit found for CCP used as PEP, as opposed to the successful use of mAbs (with a much higher content of specific antibodies) in the same context. A possible explanation is that the amount of specific antibodies contained in 10 mL of C19-IG20% may not be sufficient to prevent mild COVID-19 symptoms involving the upper respiratory tract, although it may have been able to prevent progression to severe disease. The combination of casirivimab/imdevimab contains 1.2 g of SARS-CoV-2-specific immunoglobulins, a higher amount than the 200 mg and 400 mg of polyclonal immunoglobulins contained in the 1 g (5 mL) and 2 g (10 mL) doses of C19-IG20%, respectively. Our findings showing no change in viral load in nasopharynx, in contrast with the reduction observed with mAb, also supports this hypothesis. A maximum volume of 10 mL was administered in our clinical trial based on data from previous studies of other subcutaneous hyperimmune immunoglobulin products that are safe and tolerable. Nonetheless, new delivery system designs may enable larger volume subcutaneous infusion viability and tolerability. Intravenous administration could also accept higher volumes; for instance, 400 mg/kg body weight and 3.5 g administered in the ITAC[38] and OTAC (NCT04910269) studies, respectively. However, subcutaneous therapies are more likely to be successfully deployed in community and primary care settings, particularly in countries with limited healthcare systems. Regarding neutralizing activity, plasma for C19-IG20% was collected in the United States from the second half of 2020, before the emergence of alpha variant, while the trial enrolled participants in Spain from April to December 2021, during alpha and delta variants dominance periods. Analyses conducted using pseudoviral neutralization assays identified a two to three fold reduction in neutralizing antibody titres for the circulating variants. In light of this results, we cannot rule out the possibility of clinical efficacy if higher doses of C19-IG20% and/or higher neutralization capacity had been administered.

Our clinical trial has several limitations. Firstly, the trial was terminated early by the data safety monitoring board based on an interim analysis showing no signs of potential benefit to the target population; hence the target sample size was not achieved. However, based on the interim analysis results, including the lack of differences in all pre-defined efficacy endpoints, we do not expect the analysis with the target sample size to yield different conclusions. Second, recruitment was conditioned by the widespread availability of vaccines during the study period, as vaccinated individuals were not eligible to participate. Third, although all participants were required to have a positive test for SARS-CoV-2 to enrol in the study, 26% tested negative by PCR at baseline and 19% at any time during the study. It is possible that some of these asymptomatic participants were diagnosed at the end of their infectious period and viral clearance occurred between diagnosis and randomization. Another explanation might be a false positive diagnostic test, which is more frequent in the context of screening asymptomatic individuals.[41,42] However, the sensitivity analyses on baseline PCR-positive participants did not change the trend of the m-ITT analysis. Regarding key clinical endpoints such as hospitalisation and need for oxygen supplementation, we were unable to draw any strong conclusions due to the low frequency of these events and the relatively small sample size, which limited the statistical power of the analysis. Another limitation is that the study was conducted mainly in unvaccinated patients, most of whom were seronegative at baseline. Also, our trial included 80% of participants with no comorbidities and none of them were immunocompromised. It remains unknown whether this intervention could benefit individuals at higher risk in the absence of other therapies with proven efficacy. Finally, the reduction in neutralization activity of the C19-IG20% against different circulating variants at the time of infusion may have contributed to lack of efficacy, indicating the importance of developing agile production and distribution workflows for hIG therapies, so that they can be administered timely.

On the other hand, several aspects of the methodology and study conduct strengthen and increase the generalizability of our findings. First, this is the first controlled clinical trial to report results of anti-COVID-19 hIG as treatment of ambulatory SARS-CoV-2 infected individuals. The trial included a large and diverse trial population that was enrolled at different sites throughout Spain. In addition, intervention was double-blinded, with a very high percentage of participants receiving the infusion and completing the follow-up. Finally, the main results of our trial regarding clinical efficacy are supported by virological and laboratory endpoints, contributing to more robust conclusions about the potential effect of C19-IG20%.

The results of this trial do not support the use of the subcutaneous human hyperimmune immunoglobulin C19-IG20% at either 1 g or 2 g dose regimen for the prevention of symptomatic COVID-19 in asymptomatic individuals with confirmed SARS-CoV-2 infection. Our findings indicate that C19-IG20% at the dose of 1 g and 2 g is safe and well tolerated. Future studies shall investigate the potential benefits of C19-IG20% and other hIG therapies with higher antibody dose and neutralizing activity in other scenarios, such as prevention of disease progression in outpatients with COVID-19, particularly those that are immunocompromised.

Contributors

OM, EM, AA, PMM, MCM conceived and designed the study. All author acquired, analysed, and interpreted the data. DO, YT did the statistical analysis. AA and OM drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors were responsible for the final decision to submit the manuscript for publication. All authors have seen and approved the manuscript. OM, AA, DO, MT had full access to and verified the data.

Data sharing statement

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) are available from the corresponding author on reasonable request.

Declaration of interests

EM, MT, NC, AS, and YT were employees from Grifols. The rest of authors declared no conflict of interest.

Acknowledgements

This study was funded by Grifols. We thank all the trial participants who volunteered for this trial; all the investigational site members involved in this trial (listed in the Supplementary Appendix) and the personnel from the Fight Aids and Infectious Diseases Foundation, ISGlobal, Gerència Territorial Metropolitana Nord (ICS), Gerència Territorial de Barcelona (ICS), Gerència Territorial Metropolitana Sud (ICS), Gerència Territorial de la Catalunya Central (ICS), Gerència Territorial de Girona (ICS) and Gerencia Asistencial de Atención Primaria de Madrid for their support and contributions. We thank Gerard Carot-Sans for providing medical writing support with manuscript preparation. We also thank Laia Bertran, Mireia Clua, Jordi Mitjà, Sergi Gavilan and Joan Mercado for the operational management of the project. We thank Lydia Martinez, Marta José, Jordi Bozzo and Sandra Camprubí from Grifols. We thank the members of the external data monitoring board for their time and dedication. We thank Patricia Armenteros, Ainoa Rueda, Jordi Ruiz Camp, Diego Vergara, Ana Álvarez, Ramón Mascaró, Nuria Navarro, Paula Campello, María Galán, Cristina Aragüés. ISGlobal receives support from the Spanish Ministry of Science and Innovation through the Centro de Excelencia Severo Ochoa 2019–2023 Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the Centres de Recerca de Catalunya Program. Centro de Investigación en Salud de Manhiça is supported by the Government of Mozambique and the Spanish Agency for International Development. OM was supported by the European Research Council under grant agreement number 850450 (European Union's Horizon 2020 Research and Innovation Program, ERC-2019-STG funding scheme).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101898.

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